

# BREAST CANCER

## OVERVIEW

- Approximately 200,000 new cases in the U.S. each year; recent increase in incidence largely due to smaller primary tumors being discovered through *screening mammography*.
- Most common cancer in women; second most common cause of death from cancer (after lung cancer) in women.
- Two thirds of patients with breast cancer have no evidence of lymph node involvement at diagnosis.

## UNIQUE FEATURES

- Important *prognostic factors* in breast cancer include size of primary breast lesion, presence of axillary adenopathy, number of axillary nodes involved with cancer, tumor differentiation (cytoplasmic and nuclear grade), presence or absence of hormone (estrogen and progesterone) receptors.
- For women with small breast cancers ( $\leq 1$  cm maximum diameter) without axillary involvement, the long-term survival is excellent (9% recurrence at 10 years).
- The extent of axillary node involvement is the *strongest* predictor of risk for recurrence and of survival. For example, independent of tumor size, 70% of women with *negative* axillary nodes at the time of surgery survive 10 years. In contrast, for women treated with surgery only (no adjuvant chemotherapy), 10-year survival with 1-3 involved axillary nodes is 40%, as compared with only 15% for women with  $>4$  involved nodes.
- While morphologic tumor type does not appear to have an important effect on prognosis, independent of those factors noted above, the less common breast tumor types (e.g., tubular, mucinous, papillary carcinoma) appear to have an overall superior prognosis.

## DIAGNOSTIC EVALUATION

### Screening -

- Brief history and physical examination of the breast, followed by mammography.

### Presence of Breast Lump

- History and complete physical examination (focusing on breast, axilla) followed by mammography (for evidence of tumor multicentricity or bilateral breast involvement). In addition, routine complete blood count, liver function tests, and chest film are appropriate.

There is *no* indication that routine liver or bone scans or CT of the abdomen or chest provides additional information in asymptomatic patients with normal liver function tests and a normal chest film.

### Evidence of Potential Metastatic Spread

- Patients with any indication of metastatic tumor involvement at presentation should have appropriate diagnostic tests. For example, those with bone pain or elevated alkaline phosphatase should have a bone scan.

## STAGING (TNM System)

### Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*: intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumor (Paget's disease with tumor is classified according to tumor size)
- T1 Tumor  $\leq 2$  cm in greatest dimension
- T1a  $\leq 0.5$  cm in greatest dimension
- T1b  $>0.5$  cm, but  $\leq 1$  cm in greatest dimension
- T1c  $>1$  cm, but  $\leq 2$  cm in greatest dimension
- T2 Tumor  $>2$  cm but  $\leq 5$  cm in greatest dimension
- T3 Tumor  $>5$  cm in greatest dimension
- T4 Tumor of any size with direct extension to the chest wall or skin
- T4a Extension to the chest wall
- T4b Edema (including *peau d'orange*) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
- T4c Both (T4a and T4b)
- T4d Inflammatory carcinoma

## Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)

## Distant Metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (also includes metastasis to ipsilateral supraclavicular lymph nodes)

## Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1,N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

## TREATMENT

### Primary Breast Cancer

Goals of primary treatment of breast cancer are removal of macroscopic tumor, treatment of microscopic local and regional disease, and to minimize morbidity of treatment (both functional and cosmetic). These goals can be successfully accomplished through several strategies, including:

- Modified radical mastectomy (breast and axillary contents removed with preservation of pectoralis muscles). This procedure may be followed by breast reconstruction.
- Partial mastectomy, axillary dissection, and breast irradiation. (Breast-preserving procedure removes all known macroscopic tumor; radiation is employed to treat residual microscopic disease.) Radiation can be by external beam only or may involve a "boost" to the area of initial tumor involvement with an interstitial implant.
- The decision to remove the breast, either partially or completely, depends on several factors, including the size of the tumor relative to the size of the breast (i.e., will the amount of residual normal breast tissue result in a favorable cosmetic result as compared with reconstruction of a new breast?), multifocal breast cancer (favoring total breast removal), and patient choice (e.g., complete removal of tissue without radiation versus partial removal and the requirement for several weeks of radiation treatment).

### Adjuvant Therapy (Hormonal or Chemotherapy)

- Data from >125 randomized trials involving >75,000 women with breast cancer have documented the role of both adjuvant chemotherapy and hormone therapy in prolonging both disease-free survival and overall survival in early-stage breast cancer. In general, chemotherapy is employed as adjuvant treatment in premenopausal women, whereas either chemotherapy or hormone therapy (or both) is employed in postmenopausal patients with breast cancer.
- In women with *node-negative breast cancer*, treatment with tamoxifen (an "anti-estrogen" hormone) resulted in a 26%  $\pm$  4% (SD) reduction in disease recurrence and a 17%  $\pm$  5% decrease in mortality. Combination chemotherapy in this setting resulted in a 26%  $\pm$  7% decrease in tumor recurrence and an 18%  $\pm$  8% improvement in survival.
- The benefits of adjuvant therapy for *node-positive breast cancer* are greatly influenced by the number of positive nodes found at surgery. The overall percent reduction in recurrence is approximately 24–30% and the decrease in mortality 15–20%.

### Treatment of Metastatic Disease

- A number of cytotoxic drugs have demonstrated significant activity against breast cancer (e.g., doxorubicin, paclitaxel, docetaxel, alkyl-

ating agents). In a woman with good performance status and relatively low tumor burden, the anticipated objective response rate to several combination regimens (e.g., cyclophosphamide, methotrexate, 5-fluorouracil (CMF); cyclophosphamide, doxorubicin, 5-fluorouracil (CAF)) is approximately 50–70%. In patients with poor performance status at the initiation of treatment, the response rate drops to 10–25%. The median duration of response in metastatic disease is 9–12 months.

- Hormone therapy (e.g., tamoxifen, megestrol acetate) is effective in women with estrogen and progesterone receptor-positive tumors. In the absence of receptor positivity, the objective response rate to a variety of hormonal regimens is <10%; however, if both receptors are present in a tumor, the response rate increases to 60–80%. As with chemotherapy, the duration of response is generally 9–12 months.
- Unfortunately, <5% of patients with metastatic breast cancer remain in remission for >10 years. Median survival for patients who fail to respond to initial chemotherapy is <6 months.

## NEW DIRECTIONS

- Additional prognostic factors have been suggested to be significant in breast cancer. These include HER-2 *neu* oncogene expression, epidermal growth factor expression, altered P53 suppressor gene, evidence of extensive angiogenesis in the tumor, and cathepsin D expression. It remains unknown at present if these factors provide clinically relevant information beyond that already obtained with knowledge of tumor grade, axillary node involvement, and hormone receptor status. These, and other new factors, remain in the clinical development stage.
- High-dose chemotherapy with bone marrow or peripheral progenitor cell support (to rescue the marrow from the myeloblastic effects of the cytotoxic agents) is a promising investigative approach to management of both metastatic breast cancer and women at high risk for developing recurrent disease. Preliminary data from nonrandomized trials of this strategy in both the metastatic and adjuvant settings suggest that survival may be prolonged, as compared with that of historical control groups.

### Suggested Additional Reading

- Bonadonna G, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med* 1995;332:901.
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- Kerlikowske K, et al. Efficacy of screening mammography; a meta-analysis. *JAMA* 1995;273:149.
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